原 著

Effects of Cardiac Sympathetic Nerve Stimulation on Coronary Artery and Myocardial Metabolism in the Dog with Coronary Stenosis

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Abstract

The effects of cardiac sympathetic nerve stimulation on the myocardium and coronary artery in the heart with acutely produced coronary stenosis were studied and compared with normal heart (N=21).

Intramyocardial pH in the inner layer of the myocardium distal to the stenosis was used to assess the myocardial ischemia. Coronary vascular resistance distal to the stenosis was calculated by coronary artery pressure distal to the stenosis and coronary blood flow through the stenosis.

Electrical stimulation of cardiac sympathetic nerve did not change the heart rate, while mean aortic pressure increased by approximately 12 mmHg and maximal rate of rise of left ventricular pressure increased by about 700 mmHg·sec^{-1} in both groups. Although coronary blood flow increased in both groups significantly, coronary vascular resistance increased in the normal heart but failed to increase in the heart with stenosis. Intramyocardial pH did not change in the normal heart, but tended to fall from 7.12±0.10 to 7.10 ±0.11 in the heart with stenosis.

These results suggested that in the heart with stenosis, cardiac sympathetic nerve stimulation increases coronary perfusion pressure and coronary blood flow through the stenosis, but the oxygen supply may have been insufficient for the myocardial oxygen demand in the inner layer distal to the stenosis, leading to worsening ischemia.

Key words : cardiac sympathetic nerve, coronary artery stenosis, myocardial metabolism

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Introduction

Increased sympathetic tone in response to cold pressor test or hand grip test is reported to contract coronary artery and cause coronary spasm[1], or to aggravate angina pectoris[2,3]. Coronary artery contraction[4,5] and other factors such as increased myocardial oxygen demand in the ischemic myocardium, due to augmented myocardial contractility by sympathetic nerve stimulation during surgery[6,7] may also aggravate the myocardial ischemia. Increase in coronary perfusion pressure due to increased blood pressure mediated by augmented myocardial contractility, on the other hand, has the possibility of improvement of myocardial ischemia. Therefore, whether or not the sympathetic nerve stimulation aggravates myocardial ischemia has remained undecided.

In the present study, we studied whether cardiac sympathetic nerve stimulation could contract the coronary artery distal to the stenosis and aggravate myocardial ischemia in the inner layer

of myocardium distal to the stenosis using thoracotomized dogs under fentanyl anesthesia.

Methods

Anesthesia was induced with 25 mg $\cdot kg^{-1}$ thiamylal iv in 21 mongrel dogs, followed by intratracheal intubation and artificial ventilation using Harvard respirator to maintain the $Paco_2$ at 40 mm Hg approximately. Anesthesia was maintained with intravenous injection of 50-100 μg fentanyl followed by a continuous infusion of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the experiment. Thoracotomy was performed through the left 5th intercostal space and pericardium was incised, and the heart was suspended in a pericardial cradle. The proximal left circumflex coronary artery was dissected free as far as the obtuse marginal branch and a snare for producing stenosis was placed around the circumflex coronary artery. An electromagnetic flow probe (MF-3200, Nihon Kohden) was placed proximal to the snare. One catheter-tip pressure transducer (MIKRO TIP SPC-370, Miller) was inserted into left ventricle via right carotid artery to measure left ventricular pressure. Another transducer was inserted into femoral artery and located in descending aorta to measure aortic pressure. The change in pressure with time was continuously derived from the left ventricular pressure signal. A 23 gauge catheter attached to the transducer (Statham P23, Gould) was inserted into the coronary artery at the branch of circumflex distal to the stenosis to measure coronary artery pressure and another 23 gauge catheter for blood sampling into the coronary vein in the same region. A pH electrode (pH Sensor, Kurare) was inserted and fixed in the inner layer of the myocardium distal to the stenosis.

The heart rate (HR), left ventricular pressure (LVP), maximal rate of LVP rise (LV dp/dt max), aortic pressure (AoP), coronary artery pressure distal to the stenosis (CoAP), coronary blood flow through circumflex artery (CBF), and left ventricular end-diastolic pressure (LVEDP) were measured. These data were put in and recorded with multi-purpose monitor (RMC-1000, Nihon Kohden). Coronary vascular resistance of circumflex artery (CVR) was calculated by the equation: CVR = mean CoAP/CBF. Intramyocardial pH was measured continuously with a pH/Pco_2 monitor (KR-500, Kurare) and recorded with multipurpose reccorder (MULTI RECORDER TI-104, IT Giken). Blood gas analysis was conducted with a gas analyzer (ABL-3, Radiometer). Oxygen content and hemoglobin were determined with a oximeter (CO-oximeter-2500, Corning). Blood lactate was measured with a auto-chemical analyzer (ACA-SX, Dupon). Myocardial oxygen uptake, oxygen uptake ratio, lactate uptake, lactate uptake ratio, and coronary venous-arterial blood CO_2 partial pressure difference ($_{CV}$-aPco_2) were calculated as the followings;

Myocardial oxygen uptake =

(arterial oxygen content-regional venous oxygen content) × CBF

Oxygen uptake ratio =

(arterial oxygen content-regional venous oxygen content)/arterial oxygen content

Lactate uptake =

(arerial lactate fraction-regional venous lactate fraction) × CBF

Lactate uptake ratio =

(arerial lactate fraction-regional venous lactate fraction)/arerial lactate fraction

$_{CV}$-aPco_2 = regional venous Pco_2-arterial Pco_2

The experiment consisted of sympathetic nerve stimulation in the normal heart and in the heart with coronary artery stenosis. Sympathetic nerve stimulation was performed on the anterior branch of left stellate ganglion at 2-5 Hz, 2 msec duration, 5-10 mV with electrical stimulator (S7272A, Nihon Kohden) to increase mean aortic pressure about 10mmHg and maintain this state for 90sec. Hemodynamic, intramyocardial pH, and myocardial metabolic data were obtained before and at the steady state after 90 sec sympathetic nerve stimulation. Coronary artery stenosis was instituted with a 50% decrease of CBF. The same measurement was repeated. During experiment,

normal saline was infused at a rate of 10 $ml \cdot kg^{-1} \cdot hr^{-1}$.

The results were statistically analyzed by repeated analysis of variance followed by paired t-test, using $p < 0.05$ as the level of significance. Data were expressed as mean ± standard deviation.

Results (table 1)

1. Effects of sympathetic stimulation on the normal heart.

Sympathetic stimulation caused a mild increase of HR and significant increase of systolic LVP and LV dp/dt max. Mean CoAP, CBF, and CVR increased significantly. Myocardial oxygen uptake and $cv\text{-}aPco_2$ increased significantly. Myocardial oxygen uptake ratio, lactate uptake and lactate uptake ratio tended to decrease, but intramyocardial pH did not change.

2. Effects of stenosis

CBF reduced about 50% at rest. HR, LVP, mean AoP, and LVEDP did not change, while LV dp/dt max significantly decreased, but slightly. CoAP decreased, however CVR distal to the stenosis did not change. Intramyocardial pH in the inner layer of the myocardium distal to the stenosis decreased significantly. Myocardial oxygen uptake, lactate uptake and uptake ratio in the myocardium distal to the stenosis decreased, and myocardial oxygen uptake ratio increased.

3. Effects of sympathetic stimulation on the heart with coronary stenosis.

Sympathetic stimulation caused no change in HR and significant increase of systolic LVP and LV

Table 1 Effects of Sympathetic Nerve Stimulation on Hemodynamics and Myocardial Metabolics in the Heart with intact coronary (Intact) and with stenotic coronary artery (Stenosis)

		Intact		Stenosis	
		control	SN stimulation	control	SN stimulation
HR	beats/min	82±25	89±27*	77±25	77±24
LVP	mmHg	121±20	137±18*	119±20	135±17*
LV dp/dt max	mmHg/sec	2532±604	3261±704*	2306±559#	3025±654*
m AoP	mmHg	94±18	106±19*	93±16	105±19*
LVEDP	mmHg	7.1±2.9	6.8±2.6	7.2±3.1	7.2±3.2
mCoAP	mmHg	88±17	101±18*	44±19#	56±28*
CBF	ml/min/100g	85.9±27.1	93.4±28.4*	47.9±18.6#	56.0±24.3*
CVR	mmHg/ml/min/100g	1.11±0.38	1.18±0.44*	0.96±0.40	1.07±0.46
RPP	beats·mmHg/min	9772±3062	12050±3674*	9081±3167	10376±3446*
PaO_2	mmHg	380.7±126.8	378.1±125.7	404.4±125.4	407.1±122.7
$PaCO_2$	mmHg	41.4±3.6	44.1±4.2	41.5±4.1	44.2±4.3
$PcvO_2$	mmHg	36.8±5.9	35.7±6.5	33.1±6.23#	33.3±6.4
$cv\text{-}aPCO_2$	mmHg	10.3±2.9	12.4±4.7*	13.2±3.9#	14.9±4.8*
pHt		7.20±0.05	7.20±0.06	7.12±0.10#	7.10±0.11
LA	mMol/L	1.7±0.8	1.4±0.8*	1.5±0.5#	1.3±0.7*
uptake	mMol/min	36.22±22.10	23.75±32.71	5.19±16.83#	0.89±25.58
uptake ratio	%	25.6±16.8	17.2±25.9	2.5±30.5#	-27.4±100.8*
O_2 uptake ratio	%	53.3±9.5	55.6±11.8	60.8±9.4#	62.3±10.1
$M\dot{V}O_2$	ml/min	8.95±3.12	10.11±3.79*	5.62±2.11#	6.72±2.69*

Values are mean ± SD n=21

#: $p<0.05$ versus control value of intact coronary artery

*: $p<0.05$ versus preceded value

HR=heart rate; LVP=left ventricular pressure; LV dp/dt max=maximal rate of rise of left ventricular pressure m AoP=mean aortic pressure; LVEDP=left ventricular end-diastolic pressure; mCoAP=mean circumflex coronary artery pressure; CBF=circumflex coronary blood flow; CVR= coronary vascular resistance; RPP=rate pressure product; $cv\text{-}aPCO_2$=coronary vein-artery CO_2 partial pressure difference; pH t=intramyocardial pH; LA=lactic acid; O_2 uptake ratio=myocardial oxygen uptake ratio; $M\dot{V}O_2$=myocardial oxygen consumption.

dp/dt max; these results were similar to that following sympathetic stimulation of the normal heart. Mean CoAP and CBF were increased significantly.

CVR tended to increase, but was not significantly different between before and after the stimulation. Myocardial oxygen uptake and cv-aPco2 increase significantly.

Myocardial lactate uptake and lactate uptake ratio tended to decrease, indicating a tendency of lactate production. Intramyocardial pH tended to decrease.

Discussion

In experimental coronary arterial stenosis, critical stenosis is defined as the severity of stenosis which does not cause reactive hyperemia. Vasodilatory reserve was thought to be exhausted more rapidly in the inner layer of the myocardium than the outer layer when ischemia located[8]. Although the blood vessels in the inner layer was reported to lose an ability to dilate when the coronary perfusion pressure was less than 50 mmHg[9], in other studies they did dilate with administration of α-bloker[10], and with administration of adenosine even when the coronary perfusion pressure was 35 mmHg[11] or 30 mmHg[12]. The severity of stenosis necessary to cause a disappearance of the coronary arterial dilatory reserve, therefore, has not been settled. Heusch et al[4] demonstrated that with decreasing coronary reserve of dilation, the degree of increase in coronary resistance in response to cardiac sympathetic nerve stimulation increaes, and that the vasoconstrictive effects of sympathetic stimulation induces ischemia in the myocardium supplied by severely stenosed coronary arteries represented as 40 % reduction of coronary blood flow. The stenosis in this expreiment was adjusted to a 50 % decrease of coronary blood floow at rest in order to exhaust the dilatory reserve of coronary artery distal to the stenosis without left ventricular dysfunction.

In the present study, coronary blood flow in the heart with intact coronary artery was increased in response to the sympathetic nerve stimulation and furthermore coronary vascular resistance was increased significantly (Fig. 1, 2).

In the coronary artery, post synaptic $\alpha 1$, $\alpha 2$[13], and β-receptors of the sympathetic never are innervated. In response to $\alpha 1$ and $\alpha 2$-receptor stimulation, the coronary artery constricts. Cardiac sympathetic nerve blockade accelerated the reactive hyperemia following coronary artery occlusion[14] and the increase of coronary blood flow and left ventricular function during exercise[15]. Even when coronary artery is maximally dilated, cardiac sympathetic nerve stimulation can contract the coronary artery[4,5,10,14,15]. Whether or not vasoconstrictive effects of sympathetic stimulation worsen the myocardial ischemia, however, has been devated[16]. Cardiac sympathetic nerve stimulation in the ischemic heart was reported to decrease coronary blood flow through the stenosis[4] and collateral blood flow[17], and to worsen the wall motion during exercise[5,18]. On the other hand, cardiac sympathetic nerve stimulation was though to constrict the blood vessels in the normal region[19-21]. Cardiac sympathetic nerve stimulation constrict the blood vessel in the outer layer and maintain the blood flow through the inner layer during exercise[21,22] and hypoperfusion[19,23], resulting that blood flow in the inner layer and inner-to-outer layer blood flow ratio were significantly greater in the innervated region than that in the symathectomyzed region during exercise or hypoperfusion[19-23].

In the present study, in response to the cardiac sympathetic nerve stimulation in the heart with coronary artery stenosis, coronary blood flow through the stenosis increased, while coronary vascular resistance did not increase and myocardial ischemia tended to worsen, bacause of tending to decrease of intramyocardial pH and myocardial lactate uptake ratio (Fig. 1, 2).

Cardiac sympathtic nerve stimulation also causes vascular dilation through the effect of metabolism by augmenting myocardial contractil-

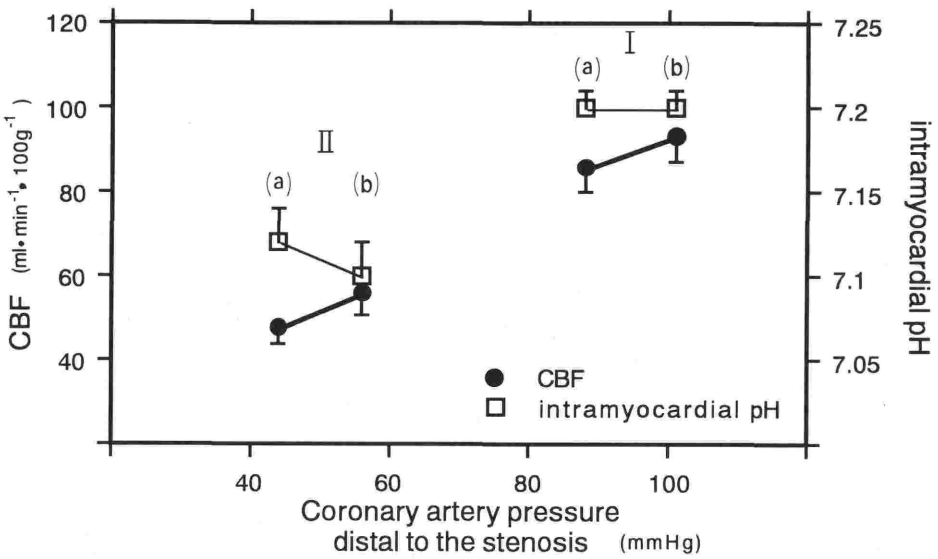

Fig. 1 Relationship between coronary artery pressure distal to the stenosis and intramyocardial pH in the inner layer of myocardium distal to the stenosis and coronary blood flow (CBF) through the stenosis.

These data are indicated in the heart with intact coronary artery (Ⅰ) and stenotic coronary artery (Ⅱ) at control state (a) and during cardiac sympathetic nerve stimulation (b). Coronary artery pressure distal to the stenosis and CBF through the stenosis increased during cardiac sympathetic nerve stimulation in both groups, while intramyocardial pH tended to decrease in the heart with stenotic coronary artery but did not change in the heart with intact coronary artery.

Data are presented as mean ± SEM; n =21.

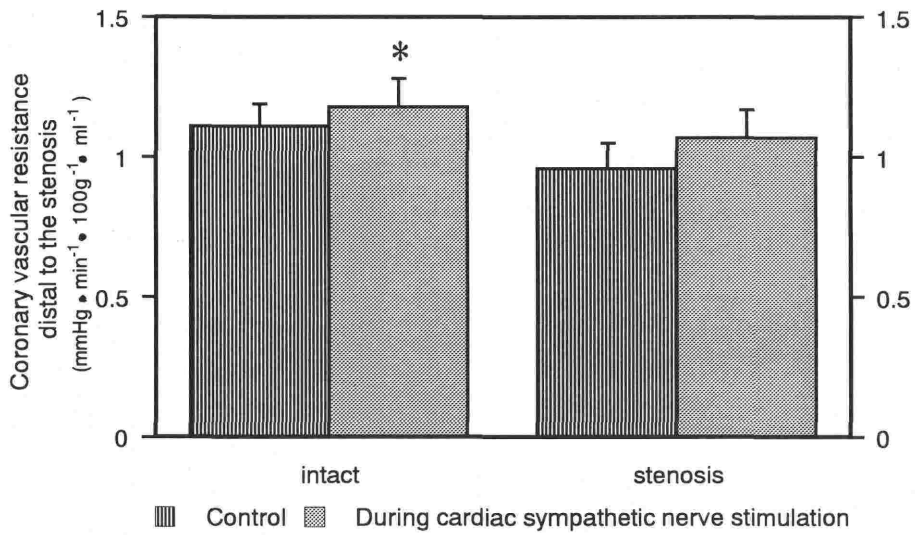

Fig. 2 Effects of cardiac sympathetic nerve stimulation on the coronary vascular resistance's of intact and stenotic coronary arteries.

Data are presented as mean ± SEM; n =21. *Significant difference from control at $P<0.05$.

ity. In the heart with severe stenosis, the dilatory reserve in the inner layer may be lost, and vasodilation in response to cardiac sympathetic nerve stimulation may be induced metabolically only in the outer layer, possibly overcoming the vasoconstriction of the alpha stimulation[6,24]. Despite of the elevation of the coronary perfusion pressure and increase of coronary blood flow in response to cardiac sympathetic nerve stimulation in this study, the blood flow may be largely diverted to the outer layer, so that the blood flow through the inner layer may become inadequate to meet the increased oxygen demand caused by augmenting myocardial contractility. This supposed to decrease intramyocardial pH in the inner layer in this study. In the heart with coronary artery stenosis, vasodilator of arterioles like adenosine is suspected to dilate the coronary artery in the outer layer, causing a transmural steal, and to aggravate the ischemia in the inner layer[23-25]. During exercise[6] and by isoproterenol administration[26], decrease in myocardial blood flow distribution in the inner layer was also reported in the ischemic heart. Katahata et al.[27] demonstrated the maldistribution of myocardial blood flow between inner and outer layer in the heart with coronary stenosis, despite the increase in coronary perfusion pressure by administration of dopamine and dobutamine for treatment of hypoperfusion developed by epidural anesthesia. These results suggested that augmentation of myocardial contractility in the ischemic heart may aggravate myocardial ischemia in the inner layer.

In patients with ergonovine-induced coronary artery contraction, norepinephrine, the cold pressor test, and the hand grip test failed to cause definite coronary vascular contraction, and α-blocker can not apparently prevent anginal attacks[28]. Thus, the participation of coronary vascular contraction in response to sympathetic stimulation in myocadial ischemia has not been established. Further studies will be necessary to clarify in this points.

Cardiac sympathetic nerve stimulation in the heart with coronary artery stenosis increased the blood flow through the stenosis, but tended to aggravate ischemia in the inner layer of myocardium distal to the stenosis. This suggested the possibility of metabolically induced vasodilation in the outer layer of myocardium and failure of the rise of the arterial pressure distal to the stenosis required to increase blood flow through the inner layer.

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